UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,277	12/04/2003	Gary J. Rosenthal	42830-10010	7142

25231 7590 09/02/2009

MARSH, FISCHMANN & BREYFOGLE LLP
8055 East Tufts Avenue
Suite 450
Denver, CO 80237

EXAMINER	
ROBERTS, LEZAH	
ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
09/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/728,277	ROSENTHAL ET AL.	
	Examiner	Art Unit	
	LEZAH W. ROBERTS	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,17,19,20,24,25,31,35,38,133-136,142,145 and 148-152* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 17, 19, 20, 24, 25, 31, 35, 38, 133-136, 142, 145 and 148-152* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/8/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed May 8, 2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office Action is made Non-Final.

Claims

Claim Rejections - 35 USC § 103 – Obviousness (New Rejection)

1) Claims 1, 17, 19, 20, 24, 25, 31, 38, 133-136, 142, 145 and 148-152

are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeck et al. (US 6,620,428) in view of Krezanoski (US 4,188,373) and Osol ed. (Remington's Phamaceutical Sciences, 1980).

Hoeck et al. disclose compositions for delivering N-acetyl cysteine transdermally. The reference discloses that it may be beneficial to deliver the N-acetyl cysteine using a transmucosal method along with the disclosed transdermal method in order to enable the drug to reach the system more rapidly when needed (col. 12, lines 1-34). The

reference differs from the instant claims insofar as it does not disclose the transmucosal delivery compositions comprise poloxamer 407 or the amount of N-acetyl cysteine used in the transmucosal compositions.

Krezanoski discloses pharmaceutical delivery vehicles comprising polyoxyethylene-polyoxypropylene to deliver active agents to the mucous membrane. The polyoxyethylene-polyoxypropylene pharmaceutical vehicles of this invention have been unexpectedly found to increase drug absorption by the mucous membrane. Moreover, it has also been found that the pharmacologic response is unexpectedly prolonged. Drug action is typically both increased and prolonged by a factor of 2 or more. At the same time, protection is afforded to the involved tissues. A preferred polyoxyethylene-polyoxypropylene block copolymer for use in the pharmaceutical vehicle of this invention is one in which the number of polyoxyethylene units is about 70% of the total number of monomeric units in the molecule, as recited in claims 138-139. "Pluronic F-127" is such a material (col. 5, lines 23-61). The pharmaceutical compositions comprise from about 10% to about 26%, preferably from about 17% to about 26% of the copolymer and from about 74% to about 90% by weight water, the vehicle having a sol-gel or gel transition temperature in the range of from about 25°C to about 40°C, preferably from about 25°C to about 35°C, and especially from about 29°C to about 31°C (col. 3, lines 1-19), which encompasses claim 137. It may be concluded that a range from 2 to 8°C the compositions will be a liquid. The compositions may also comprise components such as glycerin (Example 2). The compositions also include preservatives. In regards to the viscosity, the vehicles of the reference use overlapping

amounts of poloxamer, 10 to 20%, and water, as the compositions of the instant claims. That being said, the compositions of the reference should have the substantially the same viscosity profile as those of the instant claims. The reference differs from the instant claims insofar as it does not disclose the pharmaceutical agent is a N-acetyl cysteine.

It would have been obvious to one of ordinary skill in the art to have delivered the compositions poloxamers to deliver the N-acetyl cysteine of the primary reference motivated by the desire to increase drug absorption by the mucous membrane for rapid introduction into the system and to prolong the pharmacological response, as disclosed by the secondary reference.

The combination of Hoeck et al. and Krezanoski differs from the instant claims insofar as it does not disclose the amount of N-acetyl cysteine used it the compositions.

Osol discloses acetylcysteine is used to reduce the viscosity of pulmonary secretions and facilitate their removal. Acetylcysteine is administered by inhalation or direct instillation of a 10% or 20% solution (see page 805, second column). The reference differs from the instant claims insofar as it does not disclose the solutions comprise poloxamer 407.

It would have been obvious to one of ordinary skill in the art to have used 10% acetylcysteine in the compositions of the combined teachings of Hoeck et al. and Krezanoski motivated by the desire to use an amount of acetylcysteine effective for mucolytic activity as disclosed by Osol.

In regards to the intended use of the compositions of the combined reference, intended use carries no weight in determining patentability because it is reasonable to conclude that the compositions of the combined references would be able to treat mucositis because it comprises the same amount of acetylcysteine recited in the instant claims.

2) Claims 1, 17, 19, 20, 24, 25, 31, 35, 133-136, 142, 145 and 148-152 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeck et al. (US 6,620,428) in view of Piechota, Jr. (US 5,256,396) and Osol ed. (Remington's Phamaceutical Sciences, 1980).

Hoeck et al., the primary reference, is discussed above. The reference differs from the instant claims insofar as it does not disclose the transmucosal delivery compositions comprise poloxamer 407.

Piechota, Jr. discloses topical compositions comprising a vehicle comprising a water-soluble non-ionic block copolymer of ethylene oxide and propylene oxide, the active ingredient to be topically delivered; and water. The preferable copolymer is Poloxamer 407 and is virtually tasteless and odorless and hence has found use in solubilization of aromatics in oral hygiene products such as aqueous alcoholic mouthwashes. The poloxamer compounds are indeed known to be useful in forming gels. Poloxamer 407 is used in concentrations greater than ten percent and less than twenty percent and preferably from twelve to seventeen percent will form an aqueous single phase solution which is liquid and flowable at room temperature and will gel in

only a few seconds when elevated to about 80.degree. F. The compositions of the reference are broadly applicable to a large number of aqueous compositions intended to deliver active ingredients to a warm animal. A particular useful formulation is as a mouthwash for delivering therapeutic actives to the oral cavity. Additional components include alcohols such as ethanol, flavors, and humectants. Vehicles such as these are known in the art and there are advantages of using these vehicles[1]. In regards to the viscosity, the vehicles of the reference use overlapping amounts of poloxamer, 10 to 17%, and water, as the compositions of the instant claims. That being said, the compositions of the reference should have the substantially the same viscosity profile as those of the instant claims. The reference differs from the instant claims insofar as it does not disclose the compositions comprise N-acetyl cysteine.

It would have been obvious to one of ordinary skill in the art to have used poloxamers to deliver the N-acetyl cysteine of the primary reference motivated by the desire to increase the time the active remains at the targeted area by the formation of a gel and to use a vehicle that is virtually odorless and tasteless and is suitable for oral use, as disclosed by the secondary reference.

The combination of Hoeck et al. and Piechota, Jr. differs from the instant claims insofar as it does not disclose the amount of N-acetyl cysteine used it the compositions.

---

[1] Dobrozsi et al. (US 6,503,955) disclose vehicles such as these are known in the art and there are advantages of using these vehicles. The most commonly reported example of this type of system consists of poloxamer 407 at concentrations ranging from about 10% to 35% by weight of the composition in water. These compositions are administered at room temperature as liquids. They form a gel upon reaching body temperature. The trigger for converting these compositions to a gel, therefore, is body heat (col. 2, lines 23-36).

Osol discloses acetylcysteine is used to reduce the viscosity of pulmonary secretions and facilitate their removal. Acetylcysteine is administered by inhalation or direct instillation of a 10% or 20% solution. The reference differs from the instant claims insofar as it does not disclose the solutions comprise poloxamer 407.

It would have been obvious to one of ordinary skill in the art to have used 10% acetylcysteine in the compositions of the combined teachings of Hoeck et al. and Piechota, Jr. motivated by the desire to use an amount of acetylcysteine effective for mucolytic activity as disclosed by Osol.

In regards to the intended use of the compositions of the combined reference, intended use carries no weight in determining patentability because it is reasonable to conclude that the compositions of the combined references would be able to treat mucositis because it comprises the same amount of acetylcysteine recited in the instant claims.

Declaration under 37 CFR 1.132

1) The Declaration by Gary Rosenthal under 37 CFR 1.132 filed July 26, 2007 was sufficient to overcome the rejection of claims 15, 22-23 and 136-141 based upon Krezanoski in view of Boggs and claims 1, 15, 20, 22, 24-25, 35, 38,137, 140 and 142-148 based upon Boggs in view of Stratton.

New Rejections

The Declaration is insufficient to overcome new rejections Hoeck et al. in view of Krezanoski and Osol; and Hoeck et al. in view of Piechota, Jr. and Osol as set forth in the current Office action. The Declaration discloses why there was no motivation to combine the previously cited references. The newly cited primary reference actually teaches or suggests delivering N-acetyl cysteine transmucosally and discloses using suitable oral vehicles to accomplish this. The secondary references provide a suitable vehicle for transmucosal delivery and the effective dosage amount for N-acetyl-cysteine. Dobroszi et al. disclose these types of vehicles as being commonly used vehicles for delivering active agents (see foot note). The vehicles also comprise the amount of poloxamer recited in the amended claims. Therefore the Declaration is not sufficient to overcome the newly set forth rejections.

2) The Declaration by Antony James Mathews under 37 CFR 1.132 filed July 26, 2007 was sufficient to overcome the rejection of claims 1, 15, 19, 31, 35, 38, 133-137, 142-143 and 146 based upon Dobrozsi et al. and claims 17, 20, 24-25 and 137, 140, 144-145 and 147-148 based upon Dobrozsi et al. in view of Stratton et al.

New Rejections

The Declaration is insufficient to overcome the new rejections Hoeck et al. in view of Krezanoski and Osol; and Hoeck et al. in view of Piechota, Jr. and Osol as set forth in the current Office action. The Declaration discloses why the compositions of Dobrozsi et al. are different from the instant claims, which include the amount of

poloxamer used and the different mechanism of action. The newly cited primary reference teaches or suggests delivering N-acetyl cysteine transmucosally and discloses using suitable oral vehicles to accomplish this. The secondary references provide a suitable vehicle for transmucosal delivery. Dobroszi et al. disclose these types of vehicles as being commonly used vehicles for delivering active agents (see foot note). The vehicles also comprise the amount of poloxamer recited in the amended claims. Therefore the Declaration is not sufficient to overcome the newly set forth rejections.

3) The Declaration by Janice M. Troha was reconsidered in view of the amended claims. The Declaration is discussing intended use of the compositions and is not persuasive to overcome the rejections over Krezanoski in view of Boggs or Dobrozsi et al.

New Rejections

The Declaration is insufficient to overcome the new rejections Hoeck et al. in view of Krezanoski and Osol; and Hoeck et al. in view of Piechota, Jr. and Osol as set forth in the current Office action. The Declaration discloses N-acetyl cysteine has a different use than what is recited in the instant claims and the mechanism of action. The newly cited primary reference teaches or suggests delivering N-acetyl cysteine transmucosally and discloses using suitable oral vehicles to accomplish this. The secondary references provide a suitable vehicle for transmucosal delivery. Dobroszi et al. disclose these types of vehicles as being commonly used vehicles for delivering

active agents (see foot note). The vehicles also comprise the amount of poloxamer recited in the amended claims. Therefore the Declaration is not sufficient to overcome the newly set forth rejections.

Examiner's Response to the Declaration submitted September 29, 2006 in view of the New Rejections

In regard to the new rejections, the Examiner has previously considered and reconsidered the evidence presented by Applicant. Upon further consideration and based on the cited prior art above, the evidence presented by Applicant appears to be expected. The vehicles of Krezanoski increase in prolonged pharmacologic response, and therefore it is reasonably expected that the pharmacologically effect of the active agent, in this case acetylcysteine, would be better than the effect of the active in water or water alone. The problems of using transmucosal routes are the bioavailability. Krezanoski remedies this problem by teaching a vehicle that increases drug absorption. Since these vehicles have this property and are commonly used, it would have been obvious to one of skill in the art to use these vehicles when administering N-acetylcysteine to improve bioavailability, when a transmucosal composition is needed. Thus, there would have been a reasonable expectation of a better result. Further, it is expected that the instant composition is more effective in comparison with water and the poloxamer containing vehicle because these compositions do not comprise the active agent, N-acetylcysteine.

Obvious-Type Double Patenting (Previous Rejections)

1) Claims 1, 13, 15, 17, 19, 20, 24, 25, 31, 35, 38, 133-137, 140, 142, 143 and 145-152 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5, 6 and 8-23 of U.S. Patent No. 6,685,917. Claims 13, 15, 137, 140, 143, 146 and 147 are cancelled.

Applicant will file appropriate terminal disclaimers upon indication of allowable subject matter. The rejection is maintained.

2) Claims 1, 13, 15, 17, 19, 20, 24, 25, 31, 35, 38, 133-137, 140, 142, 143 and 145-152 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5, 6 and 8-23 of U.S. Patent No. 6,685,917 in view of Krezanoski (US 4,188,373). Claims 13, 15, 137, 140, 143, 146 and 147 are cancelled.

Applicant will file appropriate terminal disclaimers upon indication of allowable subject matter. The rejection is maintained.

3) Claims 1, 13, 15, 17, 19, 20, 24, 25, 31, 35, 38, 133-137, 140, 142, 143 and 145-152 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20, 24-30, 34-41 and 43-56 of

copending Application No. 11/540,357. Claims 13, 15, 137, 140, 143, 146 and 147 are cancelled.

Applicant will file appropriate terminal disclaimers upon indication of allowable subject matter. The rejection is maintained.

4) Claims 1, 13, 15, 17, 19, 20, 24, 25, 31, 35, 38, 133-137, 140, 142, 143 and 145-152 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6 and 8-33 of copending Application No. 11/525,752. Claims 13, 15, 137, 140, 143, 146 and 147 are cancelled.

Applicant will file appropriate terminal disclaimers upon indication of allowable subject matter. The rejection is maintained.

5) Claims 1, 13, 15, 17, 19, 20, 24, 25, 31, 35, 38, 133-137, 140, 142, 143 and 145-152 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of copending Application No. 11/605,983. Claims 13, 15, 137, 140, 143, 146 and 147 are cancelled.

Applicant will file appropriate terminal disclaimers upon indication of allowable subject matter. The rejection is maintained.

6) Claims 1, 13, 15, 17, 19, 20, 24, 25, 31, 35, 38, 133-137, 140, 142, 143 and 145-152 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 9-17, 19-21 and 23-32 of copending Application No. 11/525,983 in view of Jacob (US 2002/0103219). Claims 13, 15, 137, 140, 143, 146 and 147 are cancelled.

Applicant will file appropriate terminal disclaimers upon indication of allowable subject matter. The rejection is maintained.

Claims 1, 17, 19, 20, 24, 25, 31, 35, 38, 133-136, 142, 145 and 148-152 are rejected.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LEZAH W. ROBERTS whose telephone number is (571)272-1071. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lezah W Roberts/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612